NTP TECHNICAL REPORT

ON THE

TOXICOLOGY AND CARCINOGENESIS

STUDIES OF

COBALT SULFATE HEPTAHYDRATE

(CAS NO. 10026-24-1)

IN F344/N RATS AND B6C3F$_1$ MICE

(INHALATION STUDIES)

NATIONAL TOXICOLOGY PROGRAM
P.O. Box 12233
Research Triangle Park, NC 27709

August 1998

NTP TR 471

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

FOREWORD

The National Toxicology Program (NTP) is made up of four charter agencies of the U.S. Department of Health and Human Services (DHHS): the National Cancer Institute (NCI), National Institutes of Health; the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health; the National Center for Toxicological Research (NCTR), Food and Drug Administration; and the National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control. In July 1981, the Carcinogenesis Bioassay Testing Program, NCI, was transferred to the NIEHS. The NTP coordinates the relevant programs, staff, and resources from these Public Health Service agencies relating to basic and applied research and to biological assay development and validation.

The NTP develops, evaluates, and disseminates scientific information about potentially toxic and hazardous chemicals. This knowledge is used for protecting the health of the American people and for the primary prevention of disease.

The studies described in this Technical Report were performed under the direction of the NIEHS and were conducted in compliance with NTP laboratory health and safety requirements and must meet or exceed all applicable federal, state, and local health and safety regulations. Animal care and use were in accordance with the Public Health Service Policy on Humane Care and Use of Animals. The prechronic and chronic studies were conducted in compliance with Food and Drug Administration (FDA) Good Laboratory Practice Regulations, and all aspects of the chronic studies were subjected to retrospective quality assurance audits before being presented for public review.

These studies are designed and conducted to characterize and evaluate the toxicologic potential, including carcinogenic activity, of selected chemicals in laboratory animals (usually two species, rats and mice). Chemicals selected for NTP toxicology and carcinogenesis studies are chosen primarily on the bases of human exposure, level of production, and chemical structure. The interpretive conclusions presented in this Technical Report are based only on the results of these NTP studies. Extrapolation of these results to other species and quantitative risk analyses for humans require wider analyses beyond the purview of these studies. Selection *per se* is not an indicator of a chemical's carcinogenic potential.

Listings of all published NTP reports and ongoing studies are available from NTP Central Data Management, NIEHS, P.O. Box 12233, MD E1-02, Research Triangle Park, NC 27709 (919-541-3419). The Abstracts and other study information for 2-year studies are also available at the NTP's World Wide Web site: http://ntp-server.niehs.nih.gov.

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CONTENTS

ABSTRACT

$CoSO_4 \cdot 7H_2O$

COBALT SULFATE HEPTAHYDRATE

CAS No. 10026-24-1

Molecular Weight: 281.13

Synonyms: Bieberite; cobalt(II) sulfate (1:1) heptahydrate; cobalt monosulfate heptahydrate; cobalt(II) sulphate heptahydrate; sulfuric acid, cobalt(2+) salt (1:1) heptahydrate

Cobalt sulfate is used in the electroplating and electrochemical industries. It is also used as a coloring agent for ceramics and as a drying agent in inks, paints, varnishes, and linoleum. Cobalt sulfate may be added to animal feed as a mineral supplement and has been used as a top dressing on pasture lands. Cobalt sulfate was nominated by the National Cancer Institute for study based on a lack of information on the toxicity of soluble salts. Male and female F344/N rats and $B6C3F_1$ mice were exposed to cobalt sulfate heptahydrate (approximately 99% pure) by inhalation for 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium*. The results of prechronic inhalation toxicity studies were reported previously (Bucher *et al.*, 1990; NTP, 1991).

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female rats were exposed to aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

Survival of exposed males and females was similar to that of the chamber controls. Mean body weights of exposed male and female rats were similar to those of the chamber controls throughout the study.

Pathology Findings

The incidences and severities of proteinosis, alveolar epithelial metaplasia, granulomatous alveolar inflammation, and interstitial fibrosis were markedly greater in all exposed groups of male and female rats than in the chamber controls. The incidences of alveolar epithelial hyperplasia in all groups of exposed males and in females exposed to 3.0 mg/m^3 were significantly greater than those in the chamber control groups, as were the incidences of squamous metaplasia in 1.0 mg/m^3 females and atypical alveolar epithelial hyperplasia in 3.0 mg/m^3 females. In 3.0 mg/m^3 males, the combined incidence of alveolar/bronchiolar neoplasms (adenoma and/or carcinoma) was significantly greater than in the chamber controls. In female rats exposed to 1.0 or 3.0 mg/m^3, the

incidences of alveolar/bronchiolar neoplasms were significantly greater than those in the chamber control group and exceeded the NTP historical control ranges. A squamous cell carcinoma was observed in one 1.0 mg/m^3 and one 3.0 mg/m^3 female.

The incidences of benign, complex, or malignant pheochromocytoma (combined) in 1.0 mg/m^3 males and in 3.0 mg/m^3 females were significantly greater than those in the chamber controls and exceeded the historical control ranges.

Hyperplasia of the lateral wall of the nose, atrophy of the olfactory epithelium, and squamous metaplasia of the epiglottis were observed in all exposed groups of males and females, and the severities of these lesions increased with increasing exposure concentration. The incidences of squamous metaplasia of the lateral wall of the nose and metaplasia of the olfactory epithelium were increased in 3.0 mg/m^3 males and females.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female mice were exposed to aerosols containing 0, 0.3, 1.0, or 3.0 mg/m^3 cobalt sulfate heptahydrate 6 hours per day, 5 days per week, for 105 weeks.

Survival and Body Weights

Survival of exposed males and females was similar to that of the chamber controls. Mean body weights of 3.0 mg/m^3 male mice were less than those of the chamber controls from week 96 until the end of the study. The mean body weights of all exposed groups of female mice were generally greater than those of the chamber controls from week 20 until the end of the study.

Pathology Findings

The incidences of diffuse histiocytic cell infiltration in 3.0 mg/m^3 males and of focal histiocytic cell infiltration in 3.0 mg/m^3 females were significantly greater than those in the chamber controls. The incidences of alveolar/bronchiolar neoplasms in 3.0 mg/m^3 males and females were significantly greater than those in the chamber control groups. The combined incidences of alveolar/bronchiolar adenoma or carcinoma and the incidences of alveolar/bronchiolar carcinoma in 3.0 mg/m^3 males and females and the incidence of alveolar/bronchiolar adenoma in 3.0 mg/m^3 females exceeded the NTP historical control ranges for inhalation studies.

The incidences of atrophy of the olfactory epithelium in 1.0 and 3.0 mg/m^3 males and females and hyperplasia of the olfactory epithelium in 3.0 mg/m^3 males and females were significantly greater than in the chamber controls. Squamous metaplasia of the larynx was observed in all exposed groups of males and females.

Male mice had a pattern of nonneoplastic liver lesions along with silver-staining helical organisms within the liver, characteristic of an infection with *Helicobacter hepaticus*. In NTP studies with *H. hepaticus*-associated hepatitis, increased incidences of heman-giosarcoma were seen in the liver of male mice. In this study of cobalt sulfate heptahydrate, incidences of hemangiosarcoma were increased in exposed groups of male mice. Because of the above association, interpretation of the increased incidences of hemangiosarcoma in the livers of male mice was confounded. Incidences of lesions at other sites in this study of cobalt sulfate heptahydrate were not considered to have been significantly impacted by the infection with *H. hepaticus* or its associated hepatitis.

GENETIC TOXICOLOGY

Cobalt sulfate heptahydrate was mutagenic in *S. typhimurium* strain TA100 with and without liver S9 metabolic activation enzymes; no mutagenic activity was detected in strain TA98 or TA1535, with or without S9.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *some evidence of carcinogenic activity** of cobalt sulfate heptahydrate in male F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms. Marginal increases in incidences of pheochromocytomas of the adrenal

medulla may have been related to exposure to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* in female F344/N rats based on increased incidences of alveolar/bronchiolar neoplasms and pheochromocytomas of the adrenal medulla in groups exposed to cobalt sulfate heptahydrate. There was *clear evidence of carcinogenic activity* of cobalt sulfate heptahydrate in male and female $B6C3F_1$ mice based on increased incidences of alveolar/bronchiolar neoplasms.

Exposure to cobalt sulfate heptahydrate caused a spectrum of inflammatory, fibrotic, and proliferative lesions in the respiratory tract of male and female rats and mice.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 10. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 12.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Cobalt Sulfate Heptahydrate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Concentrations	Chamber control, 0.3, 1.0, or 3.0 mg/m^3	Chamber control, 0.3, 1.0, or 3.0 mg/m^3	Chamber control, 0.3, 1.0, or 3.0 mg/m^3	Chamber control, 0.3, 1.0, or 3.0 mg/m^3
Body weights	Exposed groups similar to chamber controls	Exposed groups similar to chamber controls	3.0 mg/m^3 group slightly less than chamber controls	Exposed groups slightly greater than chamber controls
Survival rates	17/50, 15/50, 21/50, 15/50	28/50, 25/49, 26/50, 30/50	22/50, 31/50, 24/50, 20/50	34/50, 37/50, 32/50, 28/50
Nonneoplastic effects	Lung: proteinosis (0/50, 16/50, 40/48, 47/50); alveolar epithelial metaplasia (0/50, 50/50, 48/48, 49/50); granulomatous alveolar inflammation (2/50, 50/50, 48/48, 50/50); interstitial fibrosis (1/50, 50/50, 48/48, 49/50); alveolar epithelial hyperplasia (9/50, 20/50, 20/48, 23/50) Nose: lateral wall hyperplasia (2/50, 14/50, 21/49, 20/50); olfactory epithelial atrophy (8/50, 24/50, 42/49, 48/50); lateral wall squamous metaplasia (1/50, 3/50, 5/49, 8/50); olfactory epithelial metaplasia (5/50, 1/50, 5/49, 30/50) Larynx: epiglottis squamous metaplasia (0/50, 10/49, 37/48, 50/50)	Lung: proteinosis (0/50, 36/49, 49/50, 49/50); alveolar epithelial metaplasia (2/50, 47/49, 50/50, 49/50); granulomatous alveolar inflammation (9/50, 47/49, 50/50, 49/50); interstitial fibrosis (7/50, 47/49, 50/50, 49/50); alveolar epithelial hyperplasia (15/50, 7/49, 20/50, 33/50); squamous metaplasia (0/50, 1/49, 8/50, 3/50); atypical alveolar epithelial hyperplasia (0/50, 0/49, 3/50, 5/50) Nose: lateral wall hyperplasia (1/50, 8/49, 26/50, 38/50); olfactory epithelial atrophy (5/50, 29/49, 46/50, 47/50); lateral wall squamous metaplasia (1/50, 1/49, 4/50, 10/50); olfactory epithelial metaplasia (2/50, 2/49, 3/50, 40/50) Larynx: epiglottis squamous metaplasia (1/50, 22/49, 39/50, 48/50)	Lung: diffuse histiocytic cell infiltrate (1/50, 2/50, 4/50, 10/50) Nose: olfactory epithelial atrophy (0/50, 0/50, 29/48, 48/49); olfactory epithelial hyperplasia (0/50, 0/50, 0/48, 10/49) Larynx: squamous metaplasia (0/48, 37/49, 48/48, 44/49)	Lung: focal histiocytic cell infiltrate (2/50, 5/50, 7/50, 10/50) Nose: olfactory epithelial atrophy (0/50, 2/50, 12/49, 46/48); olfactory epithelial hyperplasia (0/50, 0/50, 0/49, 30/48) Larynx: squamous metaplasia (0/50, 45/49, 40/47, 50/50)

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Cobalt Sulfate Heptahydrate

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Neoplastic effects	Lung: alveolar/ bronchiolar adenoma (1/50, 4/50, 1/48, 6/50); alveolar/ bronchiolar carcinoma (0/50, 0/50, 3/48, 1/50); alveolar/ bronchiolar adenoma or carcinoma (1/50, 4/50, 4/48, 7/50)	Lung: alveolar/ bronchiolar adenoma (0/50, 1/49, 10/50, 9/50); alveolar/ bronchiolar carcinoma (0/50, 2/49, 6/50, 6/50); alveolar/ bronchiolar adenoma, alveolar/bronchiolar carcinoma, or squamous cell carcinoma (0/50, 3/49, 16/50, 16/50) Adrenal medulla: benign, complex, or malignant pheochromocytoma (2/48, 1/49, 4/50, 10/48)	Lung: alveolar/ bronchiolar adenoma (9/50, 12/50, 13/50, 18/50); alveolar/ bronchiolar carcinoma (4/50, 5/50, 7/50, 11/50); alveolar/ bronchiolar adenoma or carcinoma (11/50, 14/50, 19/50, 28/50)	Lung: alveolar/ bronchiolar adenoma (3/50, 6/50, 9/50, 10/50); alveolar/ bronchiolar carcinoma (1/50, 1/50, 4/50, 9/50); alveolar/ bronchiolar adenoma or carcinoma (4/50, 7/50, 13/50, 18/50)
Uncertain findings	Adrenal medulla: benign, complex, or malignant pheochromocytoma (15/50, 19/50, 25/49, 20/50)	None	None	None
Level of evidence of carcinogenic activity	Some evidence	Clear evidence	Clear evidence	Clear evidence
Genetic toxicology				
Salmonella typhimurium gene mutations:	Positive in strain TA100 with and without S9 Negative in strains TA98 and TA1535 with and without S9			

EXPLANATION OF LEVELS OF EVIDENCE OF CARCINOGENIC ACTIVITY

The National Toxicology Program describes the results of individual experiments on a chemical agent and notes the strength of the evidence for conclusions regarding each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than control animals, do not necessarily mean that a chemical is not a carcinogen, inasmuch as the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential for hazard to humans. Other organizations, such as the International Agency for Research on Cancer, assign a strength of evidence for conclusions based on an examination of all available evidence, including animal studies such as those conducted by the NTP, epidemiologic studies, and estimates of exposure. Thus, the actual determination of risk to humans from chemicals found to be carcinogenic in laboratory animals requires a wider analysis that extends beyond the purview of these studies.

Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of the evidence observed in each experiment: two categories for positive results (**clear evidence** and **some evidence**); one category for uncertain findings (**equivocal evidence**); one category for no observable effects (**no evidence**); and one category for experiments that cannot be evaluated because of major flaws (**inadequate study**). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

- **Clear evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.
- **Some evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.
- **Equivocal evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.
- **No evidence** of carcinogenic activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.
- **Inadequate study** of carcinogenic activity is demonstrated by studies that, because of major qualitative or quantitative limitations, cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

When a conclusion statement for a particular experiment is selected, consideration must be given to key factors that would extend the actual boundary of an individual category of evidence. Such consideration should allow for incorporation of scientific experience and current understanding of long-term carcinogenesis studies in laboratory animals, especially for those evaluations that may be on the borderline between two adjacent levels. These considerations should include:

- adequacy of the experimental design and conduct;
- occurrence of common versus uncommon neoplasia;
- progression (or lack thereof) from benign to malignant neoplasia as well as from preneoplastic to neoplastic lesions;
- some benign neoplasms have the capacity to regress but others (of the same morphologic type) progress. At present, it is impossible to identify the difference. Therefore, where progression is known to be a possibility, the most prudent course is to assume that benign neoplasms of those types have the potential to become malignant;
- combining benign and malignant tumor incidence known or thought to represent stages of progression in the same organ or tissue;
- latency in tumor induction;
- multiplicity in site-specific neoplasia;
- metastases;
- supporting information from proliferative lesions (hyperplasia) in the same site of neoplasia or in other experiments (same lesion in another sex or species);
- presence or absence of dose relationships;
- statistical significance of the observed tumor increase;
- concurrent control tumor incidence as well as the historical control rate and variability for a specific neoplasm;
- survival-adjusted analyses and false positive or false negative concerns;
- structure-activity correlations; and
- in some cases, genetic toxicology.

NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS
TECHNICAL REPORTS REVIEW SUBCOMMITTEE

The members of the Technical Reports Review Subcommittee who evaluated the draft NTP Technical Report on cobalt sulfate heptahydrate on 11 December 1996 are listed below. Subcommittee members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, subcommittee members have five major responsibilities in reviewing the NTP studies:

- to ascertain that all relevant literature data have been adequately cited and interpreted,
- to determine if the design and conditions of the NTP studies were appropriate,
- to ensure that the Technical Report presents the experimental results and conclusions fully and clearly,
- to judge the significance of the experimental results by scientific criteria, and
- to assess the evaluation of the evidence of carcinogenic activity and other observed toxic responses.

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SUMMARY OF TECHNICAL REPORTS REVIEW SUBCOMMITTEE COMMENTS

On 11 December 1996, the draft Technical Report on the toxicology and carcinogenesis studies of cobalt sulfate heptahydrate received public review by the National Toxicology Program's Board of Scientific Counselors' Technical Reports Review Subcommittee. The review meeting was held at the National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Dr. J.R. Bucher, NIEHS, introduced the toxicology and carcinogenesis studies of cobalt sulfate heptahydrate by discussing the uses of the chemical and rationale for study, describing the experimental design, reporting on survival and body weight effects, and commenting on the chemical-related neoplastic and nonneoplastic lesions in male and female rats and mice. The proposed conclusions were *some evidence of carcinogenic activity* in male F344/N rats and *clear evidence of carcinogenic activity* in female F344/N rats and male and female B6C3F$_1$ mice.

Dr. Tyson, a principal reviewer, agreed with the proposed conclusions. Concerning the genetic mechanisms involved in murine lung tumorigenesis, he said that although a comprehensive study of K-*ras* activation was done in lung neoplasms, other molecular markers could have been assessed as well. Loss of heterozygosity or homozygous deletions on regions of chromosome 4, which are syntenic to regions of human chromosome 9p21 where frequent deletions are observed in human lung cancer, could have been studied to determine if similar mechanisms are at work in both murine and human lung tumorigenesis via exposure to this chemical. Dr. R.C. Sills, NIEHS, reported that further studies were planned with the next step being to look at loss of heterozygosity not only on chromosome 4, but also to look at chromosomes 6 and 11, where the p53 genes are located.

Dr. Ward, the second principal reviewer, agreed with the proposed conclusions. He agreed with the rationale for the exposure concentrations chosen for the 2-year studies but because there was no concentration-related body weight gain depression, he thought that rats and mice could have tolerated higher concentrations. With regard to the extensive lesions in the nasal cavity and larynx, he stated that this was a classic case showing the association between toxic and regenerative/reparative lesions resulting in no neoplasms.

Dr. Russo, the third principal reviewer, agreed with the proposed conclusions.

Dr. Tyson moved that the Technical Report on cobalt sulfate heptahydrate be accepted with the revisions discussed and with the conclusions as written for male F344/N rats, *some evidence of carcinogenic activity* and for female F344/N rats and male and female B6C3F$_1$ mice, *clear evidence of carcinogenic activity*. Dr. Russo seconded the motion, which was accepted unanimously with eight votes.